REMARKS

Claims 1-17 and 103-117 are in the application. Reconsideration and reexamination are respectfully requested.

1. Substitute Power of Attorney

By the attached Power of Attorney Applicant appoints the undersigned as attorney of record, rescinding all prior powers.

Change of the attorney, and the below-given attorney communication address, in the present application is solicited.

2. Requirement for Restriction Under 35 U.S.C. §121

A Requirement for Restriction Under 35 U.S.C. §121 has been made between inventions I-XX.

Applicants affirm their election without traverse of invention I, claims 1-17.

Added claims 103-117 are directed to Invention I.

3. Discussion of the Added Claims

Added dependent claims 103-105 may be compared with claim 8.

Added dependent claims 106-109 are dependent upon claim 105.

Added dependent claims 110-111, dependent upon claim 1, may be compared with claims 13 and 14.

Added dependent claims 112-115 are dependent upon claim 1.

Added independent claim 116 may be compared with claim 1, from which it differs only in the terminal section. The Examiner may care to familiarize himself with the sight differences between independent claims 1 and 116 before considering Applicant's arguments re: patentability over the reference art, as are contained within section 5, below.

Added independent claim 117 is of different scope than either claim 1 of claim 116, but its form may be compared with claims 1 and 116.

Support for all added claims exists within the specification. No new matter is added.

4. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-17 were rejected under 35 U.S.C. §112, second paragraph.

Indefiniteness found in claims 1-17 has been, in particular, addressed by amendment to certain language objected to by the Examiner in claims 1 and 12.

As regards claim 10, the term "giant magnetoresistive ratio sensor" is accurate, and definite in satisfaction of 35 U.S.C. §112, second paragraph. The "giant magnetoresistive effect", or GMR, as is used in devices as sensors, is the subject of patent classification class 360, subclass 326, as the Examiner may observe from the attached print out.

This **is** the proper name of the effect. The word "giant" -- although originally adapted in reference to the size of the effect -- is **not** an ambiguous qualifier of the size of the effect; the effect is simply, properly and universally called the "giant magnetoresistive effect".

The rejection of claim 10 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

5. Rejections Under 35 U.S.C. §§102 and 103

Claims 1-14 and 16-17 were rejected under 35 U.S.C. §102(b) over the reference art of Baselt.

Claims 1-14 and 16-17 were rejected under 35 U.S.C. §102(b) over the reference art of Shieh, et al.

Claim 15 was rejected under 35 U.S.C. §103(a) over the reference art of Baselt or of Shieh, et al., in consideration of the reference art of Moeremans, et al.

5.1 35 U.S.C. §102(b) Is an Improper Basis for Rejection

35 U.S.C. §102(**b**) is an improper basis for rejection of Applicant's claims over **either** the patent of Baselt, or of Shieh, et al., because **neither** patent was published (issued) "more than one year prior to... [Applicant's] date of application for patent in the United States".

The reference patent of Baselt issued November 9, 1999; the reference patent of Shieh, et al., issued May 2, 2000. **Neither** date is more than one year prior to Applicant's filing date of August 18, 2000.

The Examiner's 35 U.S.C. §102 rejections are assumed to be under 35 U.S.C. §102(**a**).

5.2 Applicant Argues the Rejections in the Alternative

Applicant presents **two** following arguments re: the patentability of his claims, **in the alternative**. The first argument is that the prior art taken in any combination neither teaches nor suggest Applicant's invention as now claimed. The second argument is that Applicant provides an AFFIDAVIT UNDER RULE 131 swearing behind **both** primary references.

The Examiner should regard **both** arguments, reaching the second argument only if the first argument is not sufficient to secure allowance, and then only for such claims are unallowable under the first argument. **Some** claims may be allowable under the first argument, for example claims 1-17 and 103-115, while another claim or claims, for example claim 116, may be allowable only under Applicant's second argument.

If the Examiner is unfamiliar with the procedure, he should inquire of his supervisor.

5.2.1 Rejection of Claims 1-14 and 16-17 Under 35 U.S.C. 102 over the Reference Patent of Baselt

The reference patent of Baselt regards **only** a change in the

output -- meaning the presence or absence of a signal -- in and of magnetic field sensors used to detect magnetic particles covalently bound to target (bio)molecules or to sensor bound recognition agents. "A change in the output [meaning the signal magnitude] of the magnetic field sensors indicates presence [or absence] of magnetic particles bound to the sensors, and thereby indicates the presence and said concentration of target molecule in the sample. (Abstract of Baselt, last sentence).

So functioning, the BIOSENSOR USING MAGNETICALLY DETECTABLE LABEL of Baselt **neither** teaches nor suggests "determining one or more magnetic characteristics by measuring and characterizing a magnetic signal of said target-probe complex induced by said applied magnetic field **in any one or more of (1) time response, called magnetic swing time, (2) spatial orientation, and (3) hysteresis loop as is solvable for (3a) saturation magnetization, (3b) remnant magnetization and (3c) coercive force** as well as (4) magnitude...." (claim 1) (boldface added).

In simplest terms, the claimed "magnetic characteristics" which Applicant teaches, and claims, for BIOMOLECULE DETECTION WITH MAGNETIC PARTICLES include **more** than **merely** the detection of signal magnitude including the presence or absence of a signal) -- which is **all** that is taught or suggested by Baselt.

Applicant's "determining" -- being more sophisticated than the process of Baselt -- can be used to deliver slightly different, and expanded, results. Namely, "by action of the determining... [Applicant does] identify some one or more of the presence, **location, orientation** and quantity of the target-probe complex, and thus also of the one or more target molecules or molecular complexes." (claim 1) (boldface added)

5.2.2 Rejection of Claims 1-14 and 16-17 Under 35 U.S.C. 102 over the Reference Patent of Shieh, et al.

Likewise, the reference art of Shieh, et al., teaches and

suggests only the sensing, by magnitude of detected signal, the presence or the absence of a magnetic particle that has bound to a molecule. Such a detection method neither teaches nor suggests Applicant's detection, and determination, of magnetic **characteristics**, as is claimed in the claim language taught within the previous section 5.2.1.

5.2.3 Rejection of Claim 15 Under 35 U.S.C. 103 over the Reference Patents of Baselt or Shieh, et al. in Consideration of the Reference Patent of Moeremans, et al.

The reference art of Moeremans, et al., cited by the Examiner for showing the contacting of samples with colloidal metals, does nothing to overcome the deficiencies of Baselt, or of Shieh, et al., to teach or suggest more than just the magnitude of detected signal, and neither teaches nor suggests Applicant's claimed detection, and determination, of magnetic **characteristics**.

Accordingly, claim 15, dependent upon claim 1, is patentable for the same reasons as is argued for claim 1 in the preceding section 5.2.2.

5.2.4 Added Claims

Added dependent claims 103-105 are patentable for like reasons as is claim 8, and as is claim 1 discussed above.

Added dependent claims 106-109 are dependent upon claim 105.

Added dependent claims 110-111 are patentable for like reasons as are claims 13 and 14, and as is claim 1 discussed above.

Added dependent claims 112-115 are dependent upon claim 1, and are patentable for like reasons as is claim 1.

Upon initial inspection, added independent claim 116, calling for "determin[nation of] one or more magnetic

characteristics by measuring and characterizing a magnetic signal" seemingly does **not** exclude the possibility of determining "(4) magnitude" **only**. Determining **only** magnitude is, or course, akin to the showings of Baselt, and/or of Shieh, et al. **But** regard further Applicant's claimed results of his "determining": "identify[ing] the presence, location, **orientation** and quantity of the target-probe complex, and thus also of the one or more target molecules or molecular complexes. Only by such signal analysis as is taught by Applicant, and such as is neither taught nor suggested by the art of reference in any combination, is this complex, multi-faceted, identification possible.

Added independent claim 117 deals with the ability of Applicant's signal analysis to deal with multiple species of (differently) magnetically-labeled target-probe complexes simultaneously. This **multiple species** detection labeling and detection capability is neither taught nor suggested by any of the art of reference taken in any combination.

5.3 AFFIDAVIT UNDER RULE 131

Applicant submits the attached AFFIDAVIT UNDER RULE 131 to swear behind **both** references of Baselt, and of Shieh, et al.

Applicant attests to being in possession of his invention before the earliest fling date of either of these references, and attaches supportive documentary evidence.

It is also required for adequacy of the AFFIDAVIT that the (two) references -- although **putatively** showing Applicant's invention by the **Examiner's** analysis -- do not **claim** this invention (else an interference would be proper). Applicant does not herein cite the claims of the Baselt, nor of the Shieh, et al., patents, but Applicant finds that the claimed inventions of these patents are **clearly not** the same invention as is claimed by Applicant. See MPEP §715.

According to the showing of the AFFIDAVIT, the rejections

under 35 U.S.C. §102(**a**) are requested to be withdrawn.

6. Summary

The present amendment and remarks have overcome and discussed each of the bases for the rejections presented in the Office Action. No new subject matter has been introduced by the present amendment.

In consideration of the preceding amendment and accompanying remarks, the present application is deemed in condition for allowance. The timely action of the Examiner to that end is earnestly solicited.

Applicant's undersigned attorney is at the Examiner's disposal should the Examiner wish to discuss any matter which might expedite prosecution of this case.

Sincerely yours,

William C. Fuess

William C. Fuess
Registration Number 30,054

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[X] Attorney of Record
[ ] Filed Under 37 CFR §1.34(a)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date written below.

November 19, 2003	William C. Fuess	William C. Fuess
Date	Typed Name of Person Mailing Correspondence	Signature of Person Mailing Correspondence

Definition of Class 360

SUBCLASS 326– Having Giant Magnetorestrictive (GMR) or Colossal Magnetoresistive (CMR) sensor formed of a single thin film:

To Parent definition **(subclass 313)** . To *Manual* for Class 360

Subject matter wherein a single film forms an MR sensor that exhibits a large change in resistance to a small amount of magnetic flux.

Search this Class, Subclass:

Subclass **324** –324.2 , for a GMR or CMR sensor formed of multiple thin films.

CLAIMS (IN AMENDED FORM)

1. (Currently Amended) A method of assaying molecules in a sample comprising the steps of:

providing a sample that contains one or more target molecules or molecular complexes;

contacting said target with one or more probes under conditions which permit the formation of a target-probe complex, wherein the probe comprises one or more magnetic labels;

subjecting said target-probe complex to an applied magnetic field so as to induce magnetization; and

determining one or more magnetic characteristics by measuring and characterizing a magnetic signal of said target-probe complex induced by said applied magnetic field in any one or more of (1) time response, called magnetic swing time, (2) spatial orientation, and (3) hysteresis loop as is solvable for (3a) saturation magnetization, (3b) remnant magnetization and (3c) coercive force as well as (4) magnitude so as to, by action of the determining, identify some one or more of the presence, location, orientation and quantity of the target-probe complex, and thus also of the one or more target molecules or molecular complexes.

2. (Original) The method of claim 1, wherein said target molecule or molecular complex is disposed on a support.

3. (Currently Amended) The method of claim 2, wherein said target molecule or molecular complex is disposed on the support [on] in an array.

4. (Currently Amended) The method of claim 3, wherein said array [constitutes] is an addressable array.

5. (Original) The method of claim 1, wherein said probe is disposed on a support.

6. (Currently Amended) The method of claim 5, wherein said probe

is disposed on the support [on] in an array.

7. (Original) The method of claim 6, wherein said array is an addressable array.

8. (Currently Amended) The method of claim 1, wherein said determining comprises:

measuring and characterizing the magnitude of the magnetic signal resulting from magnetization [of] induced in said target-probe complex in response to said applied magnetic field.

9. (Currently Amended) The method of claim 1, wherein said determining comprises:

providing a magnetic sensor[ing means that]; and

generat[es]ing a signal with the magnetic sensor in response to said one or more magnetic characteristics.

10. (Currently Amended) The method of claim 9, wherein said generating a signal with the magnetic sensor[ing means comprises] uses a giant magnetoresistive ratio sensor.

11. (Currently Amended) The method of claim 9, wherein said determining comprises:

providing a signal processing means that generates readable output from said signal.

12. (Currently Amended) The method of claim [1] 9

wherein said target molecule or molecular complex is disposed on a support;

and wherein said determining comprises:

moving the support or the sensor one in relation to the other in one or more directions [by transportation means].

13. (Currently Amended) The method of claim 1, further comprising:

subjecting said target-probe complex to one or more of a

plurality of applied magnetic fields having different intensities.

14. (Currently Amended) The method of claim 1, further comprising:

subjecting said target-probe complex to one or more of a plurality of applied magnetic fields having different directions.

15. (Currently Amended) The method of claim 1, further comprising:

contacting the target molecule of molecular complex with a non-magnetic colloid.

16. (Currently Amended) The method of claim 1, [wherein said] further comprising:

joining the probe [is joined] to one or more colored beads, fluorescent beads, or fluorescent cells.

17. The method of claim 1, further comprising the step of detecting the presence of said target probe complex by visual, electronic or optical means.

103. (New) The method of claim 1, wherein said determining comprises:

measuring and characterizing a time response, called the magnetic swing time, of the magnetic signal resulting from magnetization induced in said target-probe complex in response to said applied magnetic field.

104. (New) The method of claim 1, wherein said determining comprises:

measuring and characterizing a spatial orientation of the magnetic signal resulting from magnetization induced in said target-probe complex in response to said applied magnetic field.

105. (new) The method of claim 1, wherein said determining comprises:

measuring and characterizing the hysteresis loop exhibited by the magnetic signal resulting from magnetization induced in said target-probe complex in response to said applied magnetic field.

106. (New) The method of claim 105 wherein measuring and characterizing of the hysteresis loop solves the saturation of the target-probe complex, and thus said one or more of the presence, location, orientation and quantity of the target-probe complex.

107. (New) The method of claim 105 wherein measuring and characterizing of the hysteresis loop solves the saturation magnetization of the target-probe complex, and thus said one or more of the presence, location, orientation and quantity of the target-probe complex.

108. ((New) The method of claim 105 wherein measuring and characterizing of the hysteresis loop solves the remnant magnetization of the target-probe complex, and thus said one or more of the presence, location, orientation and quantity of the target-probe complex,

109. (New) The method of claim 105 wherein measuring and characterizing of the hysteresis loop solves the coercive force of the target-probe complex, and thus said one or more of the presence, location, orientation and quantity of the target-probe complex.

110. (New) The method of claim 1, further comprising:

subjecting said target-probe complex to one or more of a plurality of applied electric fields having different intensities.

111. (New) The method of claim 1, further comprising:

subjecting said target-probe complex to one or more of a plurality of applied electric fields having different directions.

112. (New) The method of claim 1 wherein the contacting of said

target is with one or more probes containing a ferromagnetic material as the magnetic label.

113. (New) The method of claim 1 wherein the contacting of said target is with one or more probes containing a ferrimagnetic material as the magnetic label.

114. (New) The method of claim 1 wherein the contacting of said target is with one or more probes containing a paramagnetic material as the magnetic label.

115. (New) The method of claim 1 wherein the contacting of said target is with one or more probes containing a superparamagnetic material as the magnetic label.

116. (New) A method of assaying molecules in a sample comprising the steps of:

providing a sample that contains one or more target molecules or molecular complexes;

contacting said target with one or more probes under conditions which permit the formation of a target-probe complex, wherein the probe comprises one or more magnetic labels;

subjecting said target-probe complex to an applied magnetic field so as to induce magnetization; and

determining one or more magnetic characteristics by measuring and characterizing a magnetic signal of said target-probe complex induced by said applied magnetic field in any one or more of (1) time response, called magnetic swing time, (2) spatial orientation, and (3) hysteresis loop as is solvable for (3a) saturation magnetization, (3b) remnant magnetization and (3c) coercive force; and (4) magnitude so as to, by action of the determining, identify the presence, location, orientation and quantity of the target-probe complex, and thus also of the one or more target molecules or molecular complexes.

117. (New) A method of assaying molecules in a sample comprising

the steps of:

providing a sample that contains a plurality of different target molecules or molecular complexes;

contacting said plurality of different target molecules or molecular complexes with a plurality of probes under conditions which permit the formation of a corresponding plurality of different target-probe complexes, wherein each probe comprises one or more magnetic labels different at least in part from magnetic labels of all other probes;

subjecting all target-probe complexes to a common applied magnetic field so as to induce magnetization concurrently in at least two of the plurality of target-probe complexes;

deriving a signal induced by said magnetic field in the at least two of said different target-probe complexes, collectively and in combination; and

analyzing the derived magnetic signal in any one or more of (1) time response, called magnetic swing time, (2) spatial orientation, and (3) hysteresis loop as is solvable for (3a) saturation magnetization, (3b) remnant magnetization and (3c) coercive force; and (4) magnitude so as to identify and characterize each and all of the at least two different target-probe complexes, thus also identifying and characterizing the different ones of the target molecules or molecular complexes that are within these at least two different target-probe complexes;

wherein at least two different molecules or molecular complexes are identifiable, and characterizable, at the same time, and by being subjected to the same magnetic field.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: John S. FOX	)	Confirmation No.: 6732
Serial No.: 09/641,667	)	Group Art Unit: 1641
Filed: August 18, 2000	)	Examiner: CHEU, Changhwa
For: **High sensitivity biomolecule detection with magnetic particles**	)	
Atty's Docket No.: FOX 0001P	)	

San Diego, California
November 19, 2003

AFFIDAVIT UNDER RULE 131

I, John S. Fox, do affirm and say:

1. I invented the invention that is taught within the above-identified patent application, and that is presently claimed, at least as early as September 3, 1994, and I thereafter proceeded with due diligence to the test of the invention and to the filing of the above-identified patent application.

2. On May 21st, 1994 I outlined the basic technology for detection of DNA by magnetic signal using an ionic labeling system in a colloidal solution. The particles in the colloidal solution are magnetic. They are so small that they are superparamagnetic this class of solutions are called ferrofluids.

3. On page 111 in my lab notebook after May 21, 1994 and June 7th 1994. I talk about direction detection of hybridized DNA in a Southern or on a membrane.

4. In a presentation dated June 7th 1994, to Invitrogen I outlined a DNA separation system, hybridization, and antibodies.

5. On Sept. 3rd 1994 I outlined a hybridization system using the non-magnetic colloid as a blocking "buffer" of the immobilized ssDNA linked to a surface. Then the ssDNA which is labeled with the magnetic colloidal solution is allowed to bind this signal is read with a magnetic sensor.

6. On Sept. 3rd 1994 outlined a hybridization system using the magnetic colloid for setting a magnetic signal base line for the immobilized ssDNA linked to a surface, this background base line read and saved. Then the ssDNA which is labeled with the magnetic colloid solution is allowed to bind this signal is read with a magnetic sensor the saved base line is subtracted, with the net signal being used to indicate a positive hybridization event.

7. On Sept. 6th, 1994, I outlined in a business plan, Magnetic dip stick, magnetic imager, gene expression detector, diagnostic chip, and **oligo array on a (MR) chip.**

8. On Sept. 23rd, 1994, I outlined a hybridization system using biotinylated probes linked to magnetic particles.

9. On October 4th, 1994, I presented magnetic detection system to PDI Bioscience, Aurora Ontario Canada covering a Diagnostic Chip, hybridization MR sensor, magnetic imager, magnetic DNA Dip Stick Reader, biotinylation, metal linkers, larger tag size, ionic and covalent bonding.

10. On October 20th, 1994, I received the attached letter of introduction from Kenneth Liu of Dynal responding to my request for information on magnetic beads.

11. On November 3rd, 1994, I signed a Non-Disclosure between Lightools Research and Nonvolatile Electronics, Inc. (NVE) signed

by Dr. Jim Daughton, President subject magnetic detection of DNA, RNA, protein and antibodies.

12. On February 28th, 1995, my business Lightools Research submitted a SBIR grant application entitled " Magnetic Sequencing System" to the Department of Energy. The PI for this grant was to be me, John S. Fox.

13. On April 14th, 1995. my business Lightools Research submitted a SBIR grant application entitled " A Novel Method for DNA Sequencing" to the NIH. The PI for this grant was to be me, John S. Fox.

14. On April 14th, 1995, Lightools Research submitted a SBIR grant application entitled " A Novel Method for DNA Detection and Measurements" to the NIH. The PI for this grant was to be me, John S. Fox.

15. On May 26th, 1995, I made my first experiment using ferrofluid (607 from Ferrofluidies Corp.) on a membrane binding to immobilized DNA, with the results very positive.

16. On June 1st, 1995, I received the attached letter of introduction from Robert Schneider of Nonvolatile Electronics, Inc. (NVE) responding to my request for information on GMR.

17. On June 14d, 1995, I outlined a hybridization system using the non-magnetic colloid as a blocking "buffer" of the immobilized ssDNA linked to a membrane. Then the ssDNA is allowed to bind, magnetic colloid solution is allowed to bind to the unblocked ssDNA, washed, signal is read with a magnetic sensor.

18. On June 14th, 1995, I outlined a system for separation,

movement and concentration of ssDNA and hybridized DNA.

19. On June 14th, 1995, I outlined a system for separation of ssDNA from hybridized DNA and unbound magnetic colloids by pulling by magnetic force threw a membrane with a pore size smaller then DNA and larger then the colloid.

20. On June 21st, 1995, I outlined signal enhancement size change, sample concentration into smaller area, add more particles in additional steps, sample and particle shape.

21. On Oct 12th, 1995, I started testing using a GMR (from NVE) sensor. Tested Ferrofluidies Crop. solutions mixed with other magnetic particles.

22. On Oct 16th, 1995, I performed additional testing using a GMR sensor.

23. On December 10th, 1995, I outlined a system for detection on the GMR chip, ie on chip detection.

24. On December 10th, 1995, I outlined a system for detection of DNA using a GMR chip and taking advantage of the fact that the GMR sensor from NVE "see" only one axis. I take advantage of this axis of sensitivity the GMR sensor from NVE by putting a strong magnetic source at a right angle to the read axis. This allows the maximum magnetic signal from the superparamagnetic particles which are bound to the DNA.

25. In May, 1996, I started experiments on separation, and/or concentration of DNA and/or antibodies using magnetic fields and magnetic and electrical fields.

26. On Nov. 27th, 1996, I conducted experiments using

antibodies. An antibody was attached to a colored plastic bead several antigens were labeled with a magnetic colloid were combined to a tube and allow time to bind. After binding a magnet was placed on the side of the tube in the positive tube a colored line appeared in the negative tube no colored line appeared. When the positive tube was agitated and the magnetic reapplied the colored line reappeared.

27. On Sept. 25, 1997, I outlined a system where a coil which would produce a magnetic force when a current was applied with a sensor at the center of the coil. The sample (DNA or antibodies) would be concentrated over the sensor this would speed hybridization, this location would be washed or a magnetic field applied to remove any unbound sample. This would result in real or near real time reading of sample and speed hybridization or sample binding by concentration.

28. On Sept. 25, 1997 I outlined an idea for multiplexing samples. By using different magnetic compounds with different hysteresis curves and measuring these curves as part of the detection process many samples could be detected in a single run from the same location.

29. On Sept. 25, 1997, I outlined an idea for multiplexing samples. By using different magnetic compounds with different saturation magnetization and measuring these curves as part of the detection process many samples could be detected in a single run from the same location.

30. On Sept. 25, 1997, I outlined an idea for magnetic swing. An example would be a magnetic particle unbound by a target molecule in a applied magnetic field would take time T-unbound to rotate to a new applied field axis, a bound particle would in a liquid that longer to realign T-bound. Light or magnetic signal could be

used to measure this change.

31. On Sept. 25, 1997, I outlined an idea for magnetic compound that would change during the chemical reaction of binding to the target this would change the compound from non-magnetic to magnetic. This could also be carried out by or as catalysis. This would be used for detection or separation. This chemical change could to the magnetic saturation or the hystersis is the compound.

32. On Sept 25, 1997, I came up with the idea of a fiber optic interferometer as magnetic particles bind to the fiber optic shell the magnetic force would increase this would change the light path and change the signal recorded.

33. On Oct 26, 1997, I deduced that a spinning disk produces centrifugal force and magnetic at the center would hold the sample until the centrifugal force was greater the magnetic force then the sample would move to the edge of the disk sample could be separated this way. The magnetic force could be produced be a coil and that coil could be pulsed helping to separate the sample.

34. On Oct 26, 1997, I determined that the spinning disk from above could be used to remove unbound sample from an hybridization reaction or remove mismatch hybridization.

35. On Oct 26, 1997, I determined that the spinning disk from above could be used to move unbound sample to an area for a hybridization.

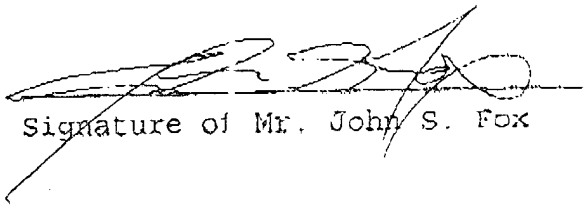
36. On Nov 26, 1997, I came up with the idea of combining the GMR sensors magnetic resistor material with a material that changes color by heat or by resistance change. Remember a

product of resistance is heat. This would be a simple system for detection of a sample that binds to a surface the sensor material the sample would bring its magnetic tag. This magnetic signal would change the resistance of the material and hence the color.

37. On March 21, 1998. I developed a magnetic sample moving system. A sample could be moved from target site to target site by a magnetic draw up system. This would take the form of a small tube with a coil around it. The coil on would pull up the sample up into the tube, coil off sample drops into the target well, draw up sample into the tube check target well for binding, on to the next target well.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

November 19, 2003
Date



Signature of Mr. John S. Fox

4/27/96 –

3:30 – turtle plastic Bead / MAE. HRP
experiment –
~~8:50~~ 8:20 – 8:50 set up samples
2 µl FF/HRP 3 tubes –
① 2 µl FF/HRP + 20 µl Goat.
② 2 µl FF/HRP + 20 µl Mouse
③ 2 µl Goat + 20 µl Mouse – Sample
Marble control –
wait 1 HR.

Wash HR pull down –
3 µl HRP + 3 µl FF to
1 ml ddH2O pull down 10 min

TWEEN 0.5% ~~Bead~~ 3 HRP 3 µl FF
1 ml ddH2O + 0.5% Tween –
Both looked like small 10 min
size particles than TBS or TBS BSA.
But some clumping.

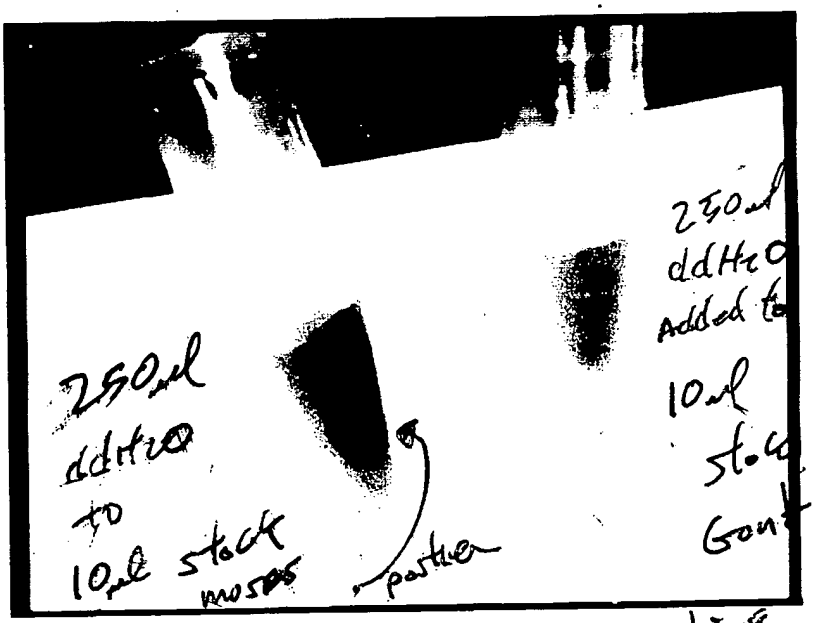
D. Thomas 11/29/96
29 NOV 96

27 NOV 96

Three Tubes mouse Ab + Goat Ab with HRP FF (From fold) stain (counter Ab) Three tubes Rabbit mouse and Goat as a negative control – for magnet attraction

2 µl HRP (FF) was added to 25 µl of Goat
2 µl HRP (FF) was added to 25 µl of MOUSE
10 µl Blue Bead (GOAT) + 10 µl Blue Bead MOUSE
negative magnet control not shown.

11/27/96

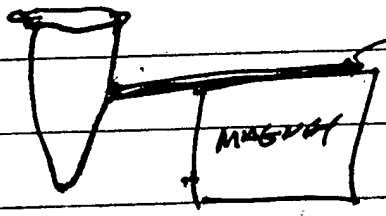


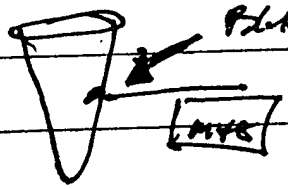
No Line

27 NOV 96

27 NOV 96.

The basic method is colored beads are coupled with a antibody mouse as a portue of Goat as a negative. Two tubes with 25ml of the stock colored beads + magnetic labled antibiss were combined and allowed to coupled for 1 hr. the two tubes were place next to a magnet, the





point of magnet

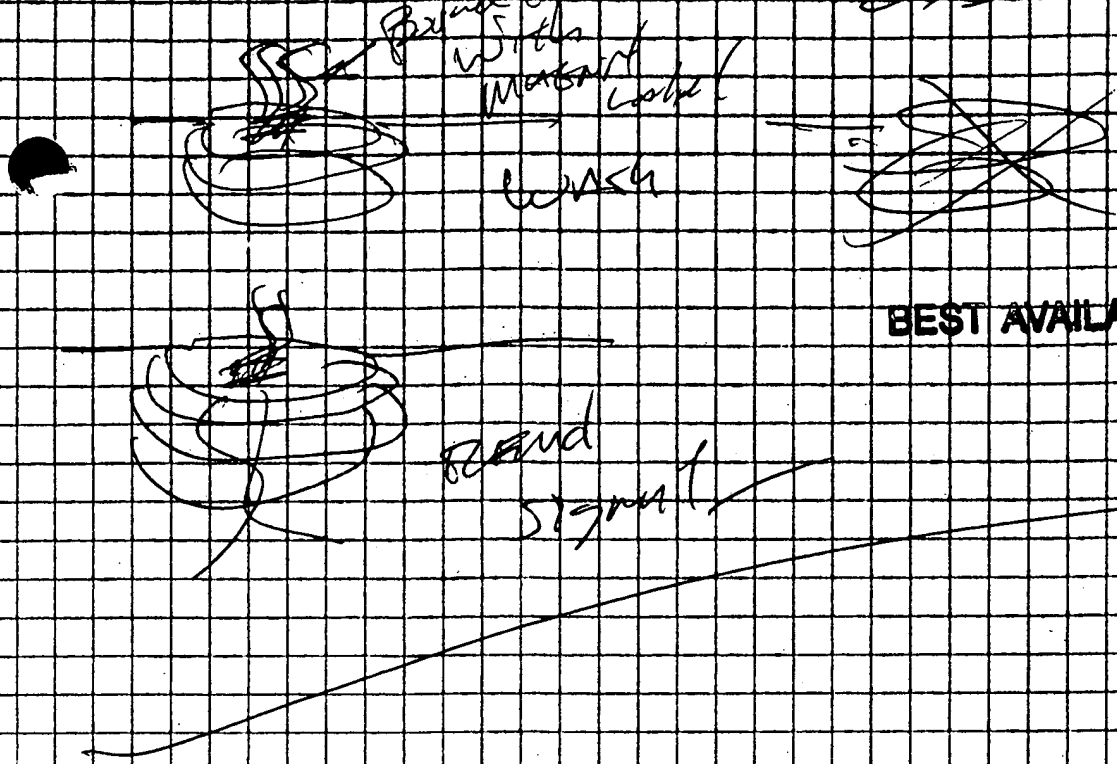
a portue formed on the more mouse tube and no the blue dot on the Goat tube.

Mouse Goat.

11/27/96

27 NOV 96

25 Sept 97



~~This system could be multiplexed by using the TD~~

On or about September 2, 1997 I came up with several additional methods for the detection of biological compounds with magnetic ~~signals~~ signals

(1) Any detection system which can be multiplexed is a system that has been improved.

One method for multiplexing would be to look at or detect the hysteresis of the magnetic compound or element used to generate the magnetic signal. By looking at the compounds hysteresis curve compounds could be screened out. A better way of stating that would over a very short time sample compounds could be measured have their hysteresis measured

9/26/97

25 Sept 97

Cont- Disert Idea

(2) The problem of multiplexing of several magnetic compounds could be ever come by measuring there saturation magnetizations of the magnetic compound or elements. Several compounds could be screened over a short time.

(3) #1 + #2 could be combined to give added degrees of freedom - #1 & #2 would be able to product not only the additive effect, but a multiplicative effect or simple counter

(4) Magnetic Swing time, ~~Magnetic~~ Swing time is defined as the time it takes for a magnetic particle to reorientate to a changing magnetic field. An example of this would be magnetic particle is aligned to a local magnetic field, this magnetic particle is in a liquid. The field is changed location is changed. The magnetic particle reorientates itself, the time to reorientate itself is the magnetic swing time. With the magnetic field held constant.

If we add mass to the magnetic particle by binding a biological particle of interest to it. Then we move

Mary Rose 9/26/97

Essert

On or about September 2 1997 I can up with several additional methods for the detection of biological molecules with magnetic signals.

1) The problem of Multiplexing of magnetic signals is over come by looking at the hystersis of the magnetic compound or element used for generation of signal by looking at the hystersis of each individual compound the signal several compounds could be screened for at any one time.

2) The problem of Multiplexing of magnetic signals is over come by looking at the stauration magnetization of the magnetic compound or element used for generation of signal by looking at the stauration magnetization of each individual compound the signal several compounds could be screened for at any one time.

3) Magnetic swing time , magnetic swing time is defined as the time it takes for a magnetic compound to reorentate it self to a changing magnetic field. If we take the case of a signal magnetic particle attached to a biological significant particle, this magnetic/bio-partical has a strong affinity for a target bio-partical. At time T0 the magnetic/bio-partical which is in a liquid as it magnetic field changed. the time to reorentate to the new field is recorded, at time T1 the target bio-partical is added to the liquid, in the case of a positive the target and the magnetic/bio-partical bind. At time T2 the magnetic field is changed the same amount as in the original measurement the time to reorentate to the new field is noted. This change in time is due the binding of the target to the magnetic/bio-particale which increases the total mass of the particle. Since the applied magnetic field id constant (FORCE) the MASS has changed the acceleration as to change to make the equation balance acceleration if a function of time.

4) Fiber optic interormtentor

5) Binding changes the partical from nonmagnetic to magnetic.

6) Binding changes the particales hystersis.

7) Binding changes the particales stauration magnetization..

9/26/97

26 Sept 97

NONVOLATILE ELECTRONICS, INCORPORATED
11409 VALLEY VIEW ROAD
EDEN PRAIRIE, MN 55344
PHONE (612) 829-9217
FAX (612) 829-9241

June 1, 1995

Lightools Research
684 Poinsetta Park South
Encinitas, CA 92024

Attn: Mr. John Fox

Dear Mr. Fox;

It was a pleasure to talk to you about your magnetic sensor needs. As I promised, I am forwarding you a copy of the presentation we made at the SENSOR EXPO in Boston recently. It addresses the multiplicity fo GMR structures and what can be expected in terms of sensor performance. NVE's primary thrust has been in the anti-ferromagnetic coupled multilayer area. Preliminary investigatiive work has begun in the spin valve area.

The very low field sensor program that we had with JPL generated a sensor that had a sensitivity of 2 micorvolts / nanotesla. We certainly would be happy to discuss your needs further. NVE will continue to develop new devices throughout 1995 and will keep you advised as to our progress. If you have any questions regarding these new sensors, please do not hesitate to let us know.

Sincerely,

Robert W. Schneider
Nonvolatile Electronics, Inc. (NVE)

2 oersteds
Device

12OCT95 —

Revive A GMR SENSOR From NVE last week - Hooked it up to A 5 volt power supply — Tested with full DST 607 DT ~~CAS~~ CAN Detect it

— I am going to set up A number to Solution 607 And Larger particals —

#1 5µl 607 + HC494 MAGNOX ~~ADDED 607~~ ADDED

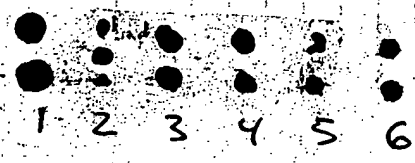
#2 5µl 607 + C440 BASE

#3 5µl 607 + 2425/42 126 BS BASE ADD 20µl CO2

#4 5µl 607 + Iron Oxide 0.014µm (M0000140XN) ADD 20µl CO2

#5 5µl 607 + Iron Oxide ~~Fe~~ Fe_2O_3 0.032µm (M000320XN) ADD 20µl CO7

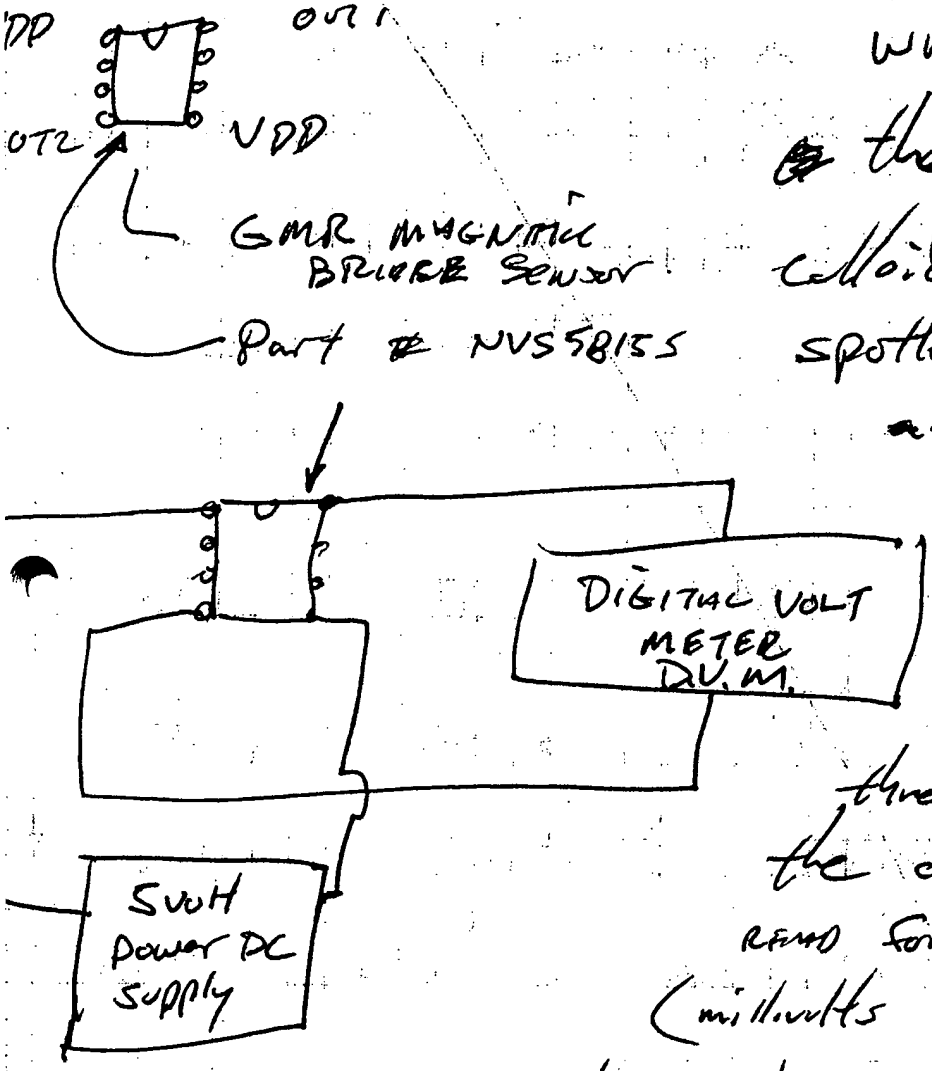
#6 5µl 607 — Control —



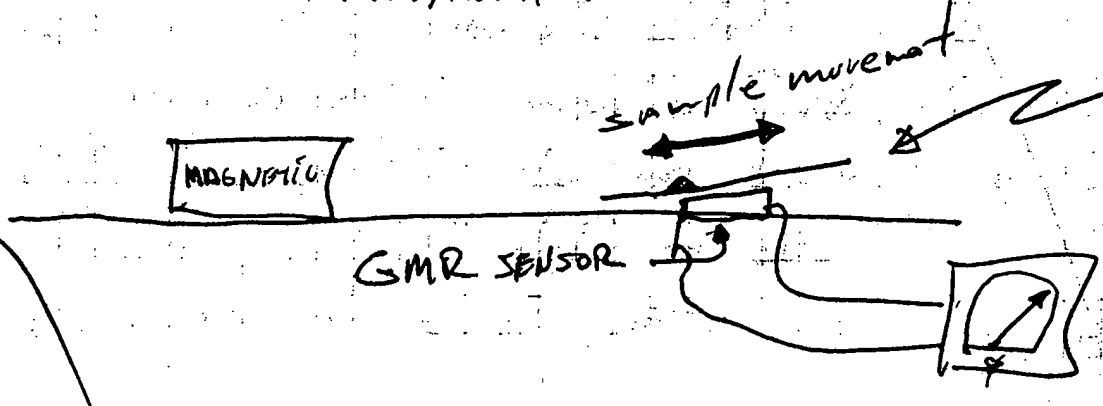
13OCT95

16 OCT 95

MAGNETIC READER SET UP.



This set up was tested with the 607 pore magnetic colloids. 607 was spotted on a membrane - and the GMR sensor was placed in a magnetic field. The sample (607 on membrane) was moved thrue the magnetic field, the change in signal was read form the D.V.M as (millivolts 0-250 ± Range) SIGNAL has a Range of ±250 millivolts.



16 OCT 95

16 OCT 95

Sample were made from the solution 1-5 on 13OCT95, and tested with the GMR sensor — Sample #1 with + Fe_2O_3 (H_c = 484) was ~~good~~ fair to poor in results, particl ~~—~~ may be to large —

Sample #2 C440, BASF, Good (RESULTS)

Sample #3 CR BASF 2425/92 RC, 133 — Good RESULTS.

Sample #4 M000140XN Good (RESULTS)

Sample #5 M000320XN Good RESULTS —

Sample were mixed with 607 + the Dry MAGNETIC particles. DNA samples were spoted on ~~the~~ nylons membranes ~~100ng~~; 100ng/ml (spots) — Sample were Dipped in the sample solution 607 + Dry MAGNETIC particals, under a magnetic field. to allow binding of the parikls to the DNA sample (2min) Sample washed H_2O 30 SEC — MEASURED with GMR SENSOR —

16 OCT 95

AGREEMENT FOR NON-DISCLOSURE OF PROPRIETARY INFORMATION

This Agreement is made and entered into as of the last date written below, by and between Lightools Research, (hereinafter referred to as "LIGHTOOLS"), having its principal office located at 684 Poinsettia Park South, Encinitas, California and NONVOLATILE ELECTRONICS, INC (hereinafter referred to as "Recipient"), a MINNESOTA corporation, having its principal office located at 11409 VALLEY VIEW ROAD EDEN PRAIRIE MN, with reference to the following facts, which by their recitation hereinbelow, are incorporated and made a part hereof.

RECITALS

A. LIGHTOOLS has developed proprietary information, trade secrets, manufacturing processes, and expertise concerning a system ("System") for the magnetic detection of DNA, RNA, protein, and antibodies including techniques associated therewith ("Know-How").

B. LIGHTOOLS has developed certain marketing concepts and procedural techniques concerning the System and proposes to disclose the Know-How to Recipient for the limited purpose of evaluating the suitability of entering into a business relationship.

C. Recipient is engaged in the business of MAGNETIC SENSORS and has the ability to further provide expertise and services in the commercial exploitation of the System.

D. The parties desire by this Agreement to provide for the delivery to Recipient of information, data and Know-How concerning the System, to provide for the retention of such information, data and Know-How in strict confidence for the benefit of LIGHTOOLS, to enable the parties to evaluate Recipient's interest in assisting LIGHTOOLS in the development of commercial exploitations of said System.

NOW, THEREFORE, in consideration of the mutual covenants, conditions and premises contained herein, the parties hereto agree as follows:

1. Incorporation of Recitals. Each of the Recitals A, B, C & D hereinabove are hereby incorporated as though fully restated herein, and made a part hereof.

2. Preliminary Disclosure.

LIGHTOOLS shall disclose said information, data, and know-how by oral and written communication and by submitting to Recipient drawings, specifications, instructions and other documents and tangibl items to the extent they are available and necessary to permit Recipient to carry out the

from LIGHTOOLS under this Agreement pertaining, referring or relating to said Know-How; and

b) All copi s, summaries, reports, records, descriptions, modifications, drawings, adaptations and oth r graphics, audio, video, or written material which Recipient has made from or relate to said Know-How.

6. Remedies for Breach of Non-Disclosure Provisions.

Recipient understands and agrees that the disclosure of said Know-How to any unauthorized person could result in serious and irreparable damage to LIGHTOOLS, that the remedy of law for any breach by Recipient will be inadequate, and that LIGHTOOLS shall be entitled to injunctive relief, without prejudice to any other rights and remedies to which they may be entitled.

7. General Provisions.

7.1 This Agreement shall bind and inure to the benefit of and be enforceable by all parties, and their assigns or successors.

7.2 In the event of any controversy, claim or dispute between the parties hereto, affecting or relating to the purpose of the subject matter of this Agreement, the prevailing party shall be entitled to recover from the non-prevailing party all reasonable expenses, including, but not limited to, reasonable attorney's fees and costs.

7.3 Should any provision of this Agreement be declared or determined by any court to be illegal or invalid, the validity of the remaining parts, terms, or provisions shall not be affected thereby.

7.4 Any notice provided for or required in this Agreement must be in writing and shall be deemed to have made when personally delivered or mailed by registered or certified mail, return receipt requested, to the parties at the address below indicated:

"Lightools"
John S. Fox, President
Lightools Research
684 Poinsettia Park South
Encinitas, California
92024

"Recipient"
J.M. Dinneen
[illegible]
11409 Valley View Road
EDEN PRAIRIE, MN [redacted] 55344

or at such other address or to the attention of such other person as the recipient party shall have specified by prior written notice to the sending party. Any notice hereunder

will be deemed to have been giv n wh n so delivered or mailed.

7.5 This Agreement may be executed in counterparts each of which is deemed to be an original and all of which together constitute one and the same agreement.

7.6 This Agreement shall be construed in accordance with the laws of the State of California.

"LIGHTOOLS"

Lightools Research

By: _____ Date: 3 NOVEMBER, 1994
John S. Fox, President

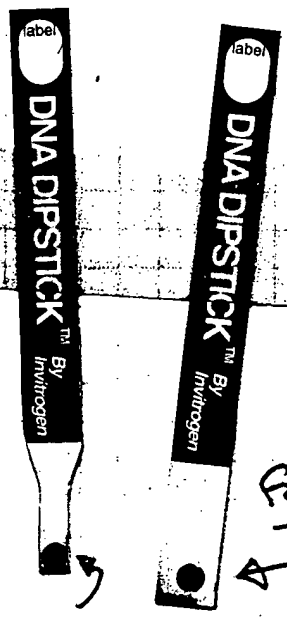
"RECIPIENT" Navigation Electronics, Inc

_____

By: _____ Date: November 3, 1994
President

Starting on Friday MAY 26th 1995 I conducted a number of experiment with a new magnetic partical.

The experimental results are as follows –
Friday MAY 26 1995 I received a package for Ferrofluidics Corp Nashua NH. There were three ferrofluides Part # 607, 605, + 807 607 + 605 where Cationic charged colloidal particals 807 is a Anionic charged colloid particals. Using a New DNA DIP Stick kit form Invitrogen San Diego CA. DNA was spotted ons the ~~the~~ DIP Stick Membrane. It was washed for 10 min ~~ad~~ ~~pot~~ put in 607 solution for 3 min, the 20 ~~sec~~ in distilled H_2O with a 4 min wash. Results were very good with a ~~large~~ large Brown Dot. When a magnet was moved ~~near~~ near the stick the stick with it The dog was attracted toward the magnet. Thus END Friday. –



Following the DNA DIP stick protocol.

Friday MAY 26th

2 June 95

10 June 95 - Arizona I-2,

There are a number of ideas that I have wanted to write down for several weeks.

(1) using the magnetic colloid system for Hybridization assays —

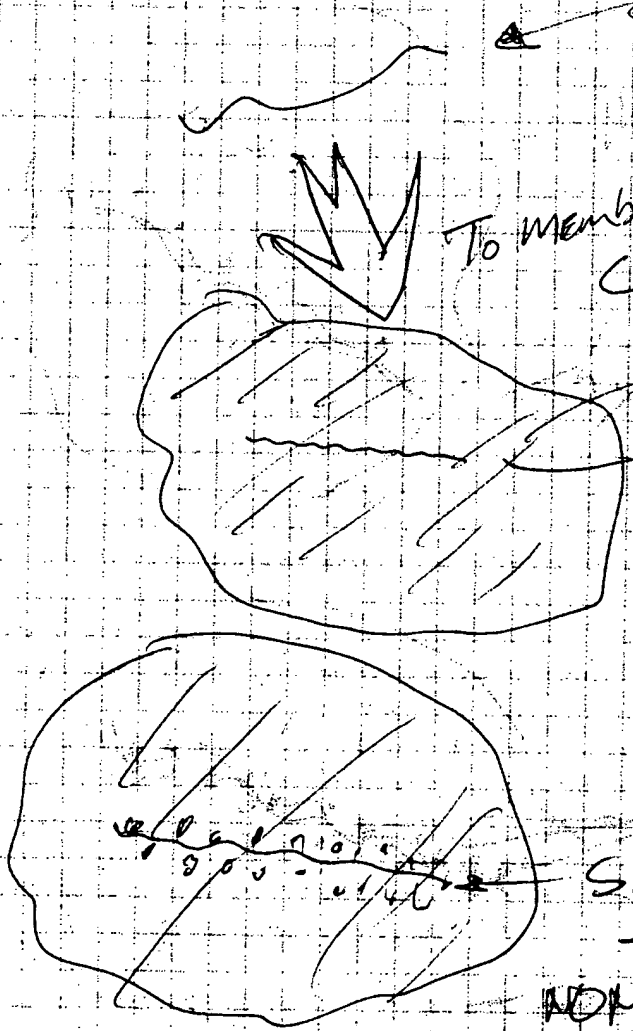
A) Link DNA to membrane —

B) wash - couple to non-magnetic colloid

C) wash - hybridize with probe —

C) Couple to magnetic colloid(s)

14 June 95

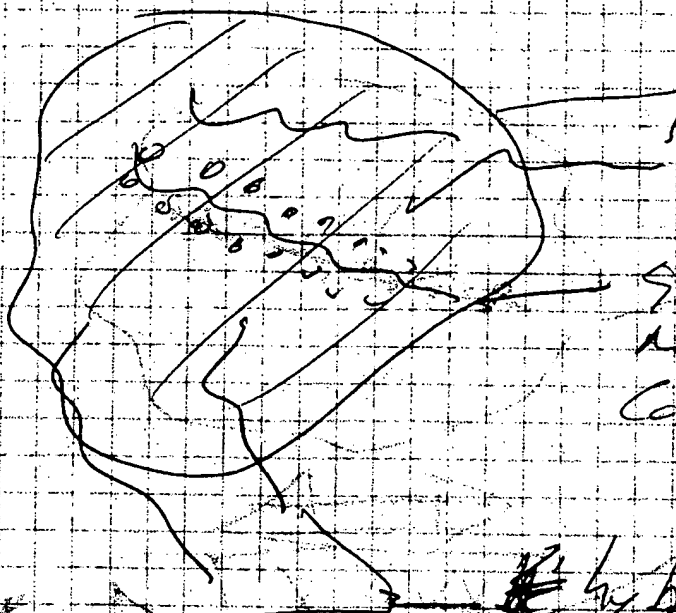


BEST AVAILABLE COPY

6/21/95

6/21/95

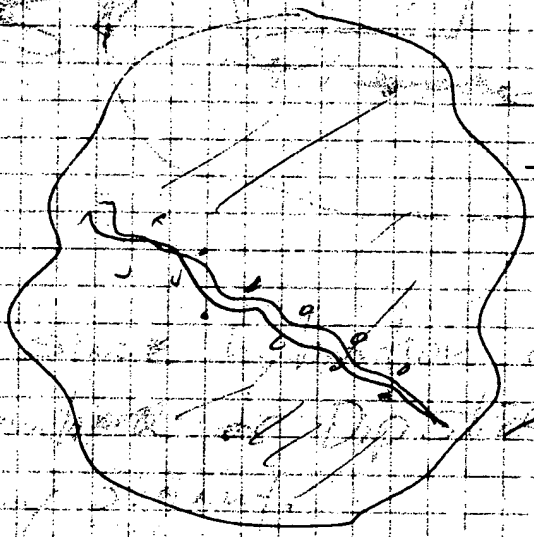
14 June 95



hybridization probes

SS DNA Target (UV) Nanomagnetic Force Control

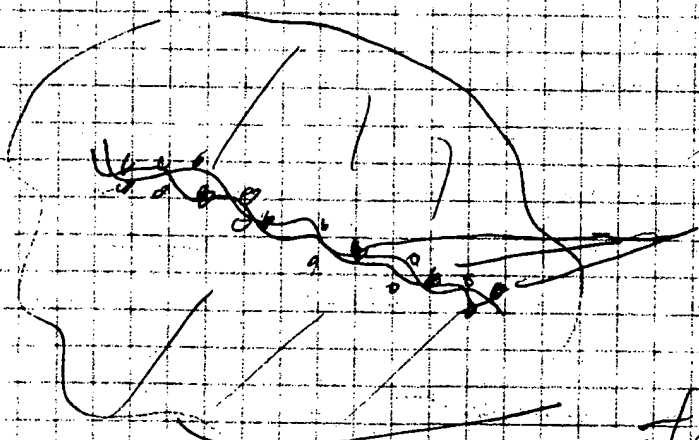
hybridization probe



Nanoparticle

hybridized control

Target DNA



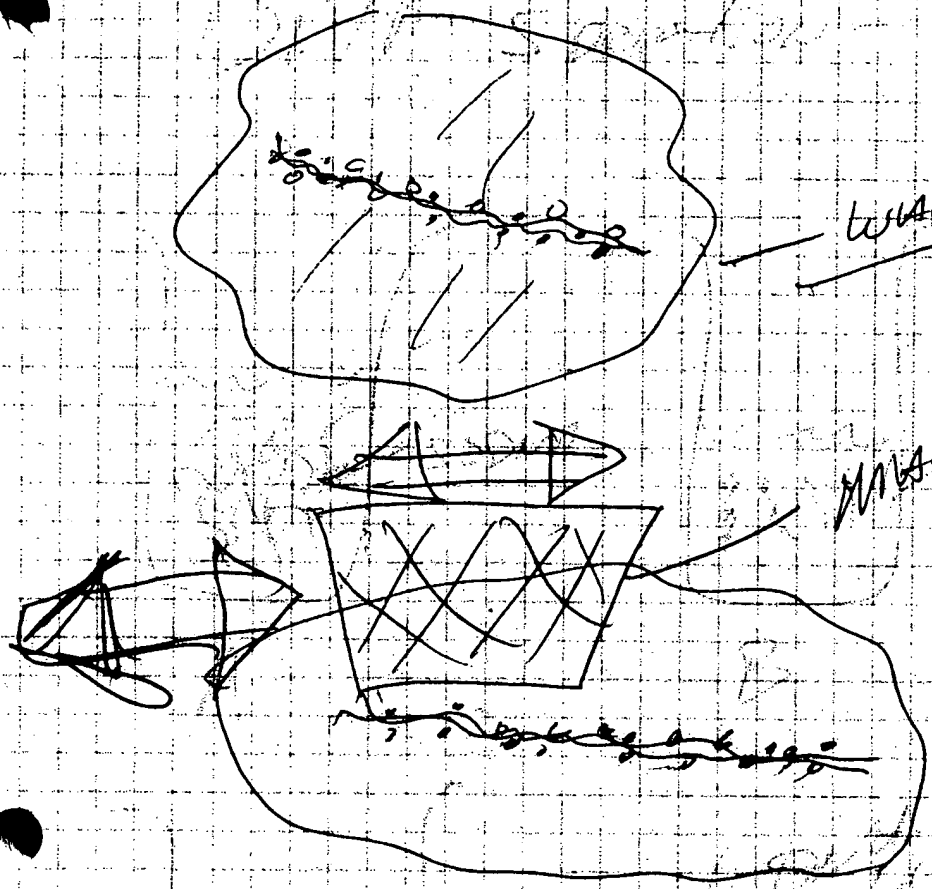
AND MAGNETIC Ionic Colloidal Solution

hard to probe DNA

6/21/95

My Docs

14 June 95



since hybridization rate yes/no & the Membrane or Dip stick will be scanned for Any signals

6/21/95

14 June 95